

## Current Understanding of Breast Cancer Risk Factors

**Khodjaeva Dilrukh Ikhomovna**

Department Assistant Bukhara State Medical Institute Bukhara, Uzbekistan

### Abstract:

Resume. This publication provides an overview of domestic and foreign literature for the period from 2011 to 2020. Risk factors for the development of malignant neoplasms of the mammary glands were analyzed. The role of the following factors is considered: genetic, chronic inflammatory and hyperplastic diseases of the genitals, reproductive function, hormonal and metabolic disorders, frustrating situations, the presence of somatic pathology, ionizing radiation, and previous surgical trauma of the breast. The results of some cohort epidemiological studies of the influence of these factors (both individual and their combinations) on the development of breast cancer are presented. Keywords: breast cancer, factors. Abstract. This review summarizes the factors of potential risk of breast cancer. Much attention was focused on genetic factor, chronic inflammatory and hyperplastic diseases of endometrium, reproductive function, hormonal and metabolic disorders, frustration, somatic pathology, ionizing radiation, before surgery. We discussed the results of some cohort and epidemiological studies of these risk factors (involvement either separate or the joint effect) in breast cancer development.

### Keywords:

breast cancer, risk factors

## INTRODUCTION

To date, the problem of breast cancer (BC) remains an extremely urgent problem around the world. In many economically developed countries, this is the most common form of cancer in women, accounting for 28.0% of all female malignancies in France, 29.0 % in the United States, 24.0 % in Sweden, and Japan— 13,9 % [13; 12; 14].

Science and innovation in In the Russian Federation, this figure was expected to reach 17.9% in 2017. Over the past 10 years, standardized incidence rates of breast cancer (BC) in the Russian Federation have been established. Deaths in Russia increased by 42.0 %, and deaths — by 43.0 %. Therefore, improving early diagnosis of breast cancer in Russia over the last decade, noted: in 2017, the detection rate for stage I and II was 62.3 %, and the proportion of advanced forms (stage III and IV) — 36,8 %. The overall 5-year survival rate for this form of tumor in Russia, accounting for 56.3 %, mortality in the 1st year of life was 10.1% [14; 13]. In Russia, the main cause of death of women of reproductive age is breast cancer [2; 11]. High levels of breast cancer morbidity and mortality make us look for new methods of preventing this pathology, based on a deep knowledge of the etiological and pathogenetic risk factors. The appearance and development of breast cancer is associated with many factors.

These reasons include heredity, factors of reproductive history, hormonal, somatic and previous diseases of the mammary glands, anthropometric, other endogenous factors, as well as environmental influences (ionizing radiation, dietary patterns, exposure to chemical and physical carcinogenic agents, etc.) [1; 11; 19; 18].

The GENETIC PREDISPOSITION FACTOR has recently become a global problem of etiology, pathogenesis, early diagnosis and prevention of breast cancer is associated with discoveries in the field of molecular genetics, which made it possible to identify genes involved in the process of carcinogenesis and determine predisposition to this disease. Hereditary changes that are inherited and highly likely to lead to cancer development are usually expressed in mutations of one allele rena-of the suppressor gene. To date , a number of suppressor genes have been identified, the congenital mutations of which lead to the development of hereditary and familial forms of malignant neoplasms (MN). Thus, the genes referred to as breast cancer genes HSCL 1, HSCL 2, inherited damage to which increases the risk of developing malignant breast tumors [19; 20]. Criteria for making a genetic diagnosis of hereditary breast cancer include the presence in the family of 2 or more relatives of the I - II degree of kinship suffering from breast cancer, the early age of the disease manifestation, bilateral mammary gland damage, the primary multiplicity of neoplasms in the proband or his relatives, specific tumor associations [1; 2; 6]. At the moment, at least 8 hereditary (monogenic) syndromes have been identified, which manifest themselves as familial pre-race.

Science and innovation lead to the occurrence of breast cancer [18; 20]. Some of the above are organ-specific: familial ovarian cancer, familial endometrial cancer, and familial breast cancer. 5 syndromes are variants of familial cancer syndrome and are manifested by a systemic predisposition to the occurrence of ovarian, breast, endometrial and some other localizations. These include familial breast/ovarian cancer syndrome; familial breast/ovarian/endometrial cancer syndrome; familial breast/ovarian/endometrial /colon cancer syndrome (Lynch2 syndrome); familial breast/endometrial/gastrointestinal/lung cancer syndrome; and familial endometrial/gastrointestinal cancer syndrome. Individuals who have inherited the breast cancer predisposition gene have a 100 % chance of developing these tumors by the age of 40-55. The general population risk of developing breast cancer, made up by 90 years of life of women, is 1.0-6.0 % [19]. It is assumed that 50.0 % of carriers of the abnormal VYASL1 gene develop breast cancer before the age of 50, and women with a personal history of breast cancer are at extremely high risk (up to 65.0 %) of developing primary contra lateral breast cancer [16]. The risk of developing ovarian cancer for such women is about 44.0% [16]. The latest literature data, which deserve special interest, were obtained in the study of R.Magleu e! al. [20], who followed 3303 women for 17 years. There is information that the presence in the family of patients of relatives of the first degree of kinship suffering from breast cancer increases the risk of developing this disease by 2.5 times both in the presence of atypical hyperplasia and without it. A burdened family history slightly increases the risk of breast cancer in women without proliferative changes in breast tissue, but in the presence of calcifications together with a burdened family history, the risk increases, which is the reason for including such women in the risk group. In the same study, it was shown that the absolute risk of breast cancer associated with atypical hyperplasia was 20.0 % within 15 years after the initial biopsy study [20]. &Magkori he pointed out the relationship of breast cancer with cystic changes in breast tissue. A small group of researchers concluded that the presence of cysts increases the risk of breast cancer in women who have relatives of the first degree of kinship, suffering from a similar disease. Such an

association was not observed among women without a family burden [11].

Science and innovation D. Coradini and M. Daidone [16] examined 25 DNA samples isolated from proliferatively altered breast tissues, including протоковыеintraductalpapillomas, for loss of heterozygosity and microsatellite instability at 10 loci, including locus D 17B 579 (area of the VYASL 1 gene), and found an incomplete correlation between genetic changes and proliferation with atypia. An important outcome of this study was that genetic changes can occur in the absence of clear clinical signs preceding malignant ones, and in these cases it is necessary to rely on a burdened family history [16]. PREVIOUS BREAST DISEASES It has been noted that the contribution of benign tumors is also significant in the development of breast cancer [15]. &Magleugh [10] observed the fate of 1,950 patients diagnosed with fibroadenoma and a combination of fibroadenomatosis and fibrocystic disease. The control group consisted of the sisters of the husbands of these women. The dynamics of the risk of developing breast cancer at a single fibroadenomas was 2.17 and increased to 3.1 in patients in the presence of combined fibroadenomas and cysts, fibroadenomas, and sclerosing of adenose, the calcification or papillomatosis, with burdened family history of accumulated 25-year risk of 20.0 %. 2/3 of patientswith single fibroadenoma and healthy relatives, risking to get sick BC along with women from the General population [11]. The risk of malignancy was determined by the degree of proliferation in fibroadenomatosis. Initial data showed that with atypical lobular hyperplasia, the risk of breast cancer increases 3-6 times, with intraductalгиперplastic processes-2 times. With cystic changes, sclerosingadenosis, and othertonon-hyperplastic changes, the risk of developing breast cancer did not significantly differ from среднепопуляционногоthe average population [10; 15]. REPRODUCTIVE FACTORS Among the etiological factors of breast cancer, a significant role belongs to gynecological diseases, primarily inflammatory processes in the uterine appendages [3; 14]. This is due to the fact that the mammary glands, as well as the uterus, are a target organ for sex hormones. A. S. Zotov notes that mastopathy is often found in hyperestrogenemia, the manifestations of which are: dysfunctional uterine bleeding, anovulatory infertility, uterine fibroids, endometriosis, ovarian follicular cysts [17]. Hormone imbalance contributes to the morphofunctional reorganization of the mammary glands, and in some women this process does not go beyond the physiological norm, while in others, under the conditions of activation of the mammary gland receptor apparatus, pathological changes are formed — mastopathy — cancer [8].

Pathological changes in the mammary glands are common in women with endometrioid heterotopias (76.0 %). With retrocervical endometriosis, they occur in 92.3 % of women, with endometrioid ovarian cysts-in 88.9 %, with adenomyosis - in 82.3 %. The frequency of nodular forms of mastopathy in such women ranges from 29.6 % to 38.5 % [12].Lapochkina demonstrated a direct correlation between mastopathy and gynecological diseases such as uterine fibroids, endometriosis, and endometrial hyperplasia [14]. Their prevalence in women with fibrocystic disease of the mammary glands exceeds 90,0 %. S. H. Ghanaiansudelat attention to the relationship of increased risk of breast cancer with late menopause and early menarche [9]. I. I. Frolova found that the occurrence of breast cancer is directly proportional to the time of occurrence of menarche and the first pregnancy and is inversely proportional to the number of children [19]. By phone, V. I. Starikova risk of breast cancer in menopause after 55 years is 2-2.5 times higher than in menopause before 45 years. On the other hand, the risk of breast cancer has been shown to decrease by 47.0 % in women with ovaries removed for various reasons under the age of 40 compared to the cohort of women with natural

menopause aged 45-54 years [17]. According to literature data, V. P. Kharchenko and N. I. Rozhkova, women who have the onset of menstruation before the age of 13, and the onset of menopause after 55 years, have a 2-2.5 times higher risk of developing breast cancer [10]. One of the most important risk factors contributing to breast cancer is the high frequency of cycles without ovulation and their hormonal manifestation — progesterone deficiency [14]. Abortion is considered an important risk factor. It not only damages the uterus, but also causes various disorders in the hypothalamic-pituitary-ovarian system, interrupts physiological proliferative processes in the mammary glands. According to many authors, it is emphasized that 3 or more abortions have a particularly unfavorable effect on the state of the breast [5; 2; 4]. According to some authors, the risk of breast cancer increases even more in the absence of childbirth and a large number of artificial and spontaneous abortions [6]. Women who give birth for the first time before the age of 18 are significantly less likely to develop breast cancer than women who give birth for the first time at the age of 35 and above [10]. Sinschyn believe that women who have had a late first birth (at the age of more than 30 years) The risk of developing breast cancer is 2 to 3 times higher than that of those who gave birth before the age of 20. Every subsequent birth before the age of 30 is accompanied by a further reduction in risk. The risk of developing breast cancer before the age of 40 is 5.3

Science and innovation are twice as high in women who gave birth at the age of more than 30 years than in those who gave birth before 20 years [8]. It is interesting that early delivery does not have a protective effect in women who have mutations of VJASL 1 or VJASL 2. Women who gave birth — carriers of mutations of VJASL 1 or VJASL 2 are significantly more likely (1.71 times) to develop breast cancer before the age of 40 than those who did not give birth. Each pregnancy is associated with an increased risk of developing breast cancer before the age of 40 [3]. S. T. Vgees has shown that preventive oophorectomy in carriers of the VYASL 1 or VYASL 2 mutations: a) reduces the risk of ovarian cancer by 96.0 %; b) reduces the risk of breast cancer by 53.0 % [7]. Numerous scientific studies that have been devoted to studying the effect of hormonal contraceptives and hormone replacement therapy on the risk of breast cancer give rather contradictory information [13]. The risk of further development of benign diseases and breast cancer increases in women who took contraceptives before the birth of their first child [12]. When using contraceptives and aborting the first pregnancy, the relative risk of developing breast cancer increases by 2.4 times [17]. GB.Fentiman notes that women who have used hormonal contraceptives for more than 5 years have a 9-fold increased risk of developing breast cancer. The use of oral contraceptives (COCs) reduces the risk of ovarian cancer and endometrial cancer by 2-3 times, without having a pronounced protective effect on breast tissue from malignant transformations [14]. Research by S. T. Brece [14] demonstrated that the incidence of breast cancer among women aged 60 years who used and did not use COCs is exactly the same. According to the latest data from the 3rd European Breast Cancer Conference (Barcelona, 2012), there was no association between oral contraceptive use and the development of breast cancer. At the same time, no correlation was found between the use of COCs and age, race, body mass index, duration of use and age of initiation of COCs, and duration of use until the first completed pregnancy [19]. There is also evidence of increased cancer risk in women over 45 years of age who continue to use COCs [13]. According to some authors, prolonged lactation is a factor that reduces the risk of cancer [17; 15], while others report a negligible effect of this factor [12]. The short duration of the lactation period (up to 5 months) is one of the risk factors for breast cancer [18].



Science and innovation **SOMATIC DISEASES** Some epidemiological studies have shown that patients suffering from breast cancer have a higher incidence of thyroid diseases than in the general population, from 9.0 % to 50.0% or more [12]. The thyroid gland has a great influence on the formation and functioning of a woman's reproductive system. Against this background, changes in the activity of the thyroid gland during critical periods of a woman's life: puberty, pregnancy, lactation, and menopause are indicated [6; 2]. If there is a pathology of the thyroid gland, it can cause premature or late puberty, amenorrhea, galactorrhea, and infertility [1,3]. There is clear evidence of a combination of changes in thyroid function with a sharp decrease in the level of yellow body hormones. There is a concept of the relationship between the function of the thyroid gland and the thyroid-stimulating function of the pituitary gland, as well as the influence of the latter on the luteinizing function of the pituitary gland. More than half (66.0%) of patients with various forms of mastopathy had thyroid pathology. Hypofunction of the thyroid gland increases the risk of breast cancer by 3.8 times [4; 5]. An important role is played by the presence of a metabolic syndrome. Insulin resistance and hyperinsulinemia as development factors of the metabolic syndrome are risk factors for the development диспластических of breast dysplastic diseases due to an increase in the level of insulin-like growth factors [6; 5]. Obesity is also accompanied by insulin resistance and, as a result, hyperinsulinemia, which contributes to an increase in the level of insulin-like growth factors in the body. Also, excess fat is a source of extra-gonadal synthesis of sex steroids, in particular androgens, which ароматазы are converted to estrogens under the influence of the aromatase enzyme, which is accompanied by hyperestrogenism, the latter, in turn, stimulates proliferative processes in breast tissues [7,18]. дисгормональной Liver diseases play a certain role in the formation of dyshormonal pathology of the mammary glands. Diseases of the hepatobiliary system most often initiate the development of chronic гиперэстроhyperestrogenism due to delayed utilization of estrogens in the liver. These data are confirmed by the high frequency of hyperplastic processes in the mammary glands in liver diseases [9; 13]. Among the risk factors mentioned are a tendency to fatness and the presence of arterial hypertension. Obesity may increase the risk of breast cancer in menopausal women and does not affect the risk in menstruating women [10; 19].

Science and innovation A number of authors have observed a link between high growth and breast cancer incidence [17]. **FRUSTRATING FACTORS** are calculated as an indicator of breast cancer risk at the social (environmental) and individual levels. There is a 1.5-fold increase in the risk of developing tumors in urban areas compared to rural areas [11]. As the quality of life of women improves, there is an increase in the incidence rate. In developed social strata, persons with higher education have a high incidence of breast cancer —  $RR = 1.7$  in relation to  $RR = 1.0$  in unskilled workers. The importance of social environment factors for the development of tumors of this localization is noted [13]. Epidemiological studies of precancerous and tumorous diseases of the mammary glands have repeatedly noted the relationship between marital status and the occurrence of these diseases. Calculations performed by L. A. Pustyrskystudies show that the relative risk of breast cancer is 1.54 times higher in unmarried women and 1.2 times higher in divorced women [14]. According to anamnestic data, only 6.9% of the total number of patients have a conflict situation at work [15]. A more unfavorable analysis was obtained in the analysis of family relationships. Out как ,of the total number, 39.8% of patients reported conflict situations at home [16]. If continuous domestic conflicts lead to a gradual accumulation of neuropsychiatric disorders, then severe sudden shocks, as a rule, cause a rapid deterioration of the clinical picture. The

proportion of patients who had severe shocks in the period preceding the examination was 14.7 % in the unmarried group and 6.3 % in the married group [11]. According to M. I. Davydov, emotional stress increases the risk of transition from a non-proliferative form of nodular mastopathy to a proliferative one by 3.3 times [10]. Today, much attention is paid to studying the influence of a woman's sexual function on the likelihood of mastopathy and breast cancer: among nuns, as well as among single women, the incidence of breast cancer is 2 times higher than in married women. Psychosexual discomfort is a powerful stressful factor [15]

Nutrition plays an important role in the etiology of ZN [16]. At least 1/3 of them are related to the nature of nutrition. Increased physical activity, both professional and sports-related, reduces the risk of cancer development [7,16, 14].

Science and Innovation Recent research has shown that alcohol consumption increases the risk of breast cancer by 1.5-2 times [15]. INJURY FACTOR According to some authors, trauma in the anamnesis of breast cancer patients is 4.7 times more common compared to the control, the presence of trauma in the anamnesis of breast cancer patients was noted in 7.33 % [11]. The authors also note the association of breast cancer with past mastitis. One of the observations indicated that in 5.7% of cases, the tumor was preceded by inflammatory processes in the mammary gland [13,15]. The influence of the factor of surgical intervention on the mammary gland is poorly studied. It is no secret that breast surgery for fibroadenoma increases the risk of breast cancer by 4 times [11].

## CONCLUSION

At the present stage, no specific risk factor for breast cancer development has been identified, since the disease is multi-factorial, associated with both genetic prerequisites and environmental influence [17]. In addition, all these factors are often found in the group of healthy women who do not develop breast cancer during their lifetime. In 4.0 - 8.0% of cases, malignant neoplasms of the breast are diagnosed in the absence of any risk factor (breast pathology, dyshormonal disease, etc.) [1,13,14]. This trend requires a more in-depth detailed study of various risk factors, detection of the most unfavorable combinations of them, and search for new, previously unknown factors that affect the development of breast cancer or prevent it.

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